UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/851,661	03/27/2013	Campbell McInnes	USC-323 (829)	8074

22827 7590 04/19/2017
DORITY & MANNING, P.A.
POST OFFICE BOX 1449
GREENVILLE, SC 29602-1449

EXAMINER
REYNOLDS, FRED H

ART UNIT	PAPER NUMBER
1675	

MAIL DATE	DELIVERY MODE
04/19/2017	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte CAMPBELL MCINNES and SHU LIU

Appeal 2016-007915
Application 13/851,661[1]
Technology Center 1600

Before ELIZABETH A. LAVIER, JOHN E. SCHNEIDER, and RYAN H. FLAX, *Administrative Patent Judges*.

LAVIER, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellants seek review of the Examiner's rejections of claims 1–5 and 7. We have jurisdiction under 35 U.S.C. § 6(b). For the reasons set forth below, we AFFIRM.

BACKGROUND

The Specification describes methods using *in silico* models to develop synthetic CDK/cyclin inhibitors, and the synthetic inhibitors generated therefrom, which may offer promise as oncology targets. *See* Spec. 3:20–22,

---

[1] Appellants state the real party in interest is the University of South Carolina. Br. 1.

4:27–28; *see generally id.* at 1:21–3:18. Claim 1, the only independent claim on appeal, is illustrative:

> 1. A method for developing a synthetic CDK/cyclin inhibitor for a first CDK/cyclin complex formed between a first CDK protein and a first cyclin protein, the method comprising:
>
> developing a first fragment ligated inhibitor from a peptide inhibitor, the peptide inhibitor including an arginine residue and a phenylalanine residue, the arginine residue being closer to the N-terminus of the peptide inhibitor than the phenylalanine residue, the peptide inhibitor inhibiting a second CDK/cyclin complex formed between a second CDK protein and a second cyclin protein, the first fragment ligated inhibitor differing from the peptide inhibitor by inclusion of a first substitute segment in place of [[the]] [sic] a first fragment of the peptide inhibitor, the first substitute segment being a non-peptide fragment, the first substitute segment comprising a capping group bonded to the arginine residue or comprising a replacement for the phenylalanine residue;
>
> determining an affinity of the first fragment ligated inhibitor for the first cyclin protein from an *in silico* model of the first fragment ligated inhibitor complexed with the first cyclin protein;
>
> based upon this affinity, modifying the first substitute segment of the first fragment ligated inhibitor one or more times to develop a second fragment ligated inhibitor comprising the modified first substitute segment, the second fragment ligated inhibitor exhibiting an increased affinity for the first cyclin protein as compared to the first fragment ligated inhibitor based upon *in silico* modeling of the second fragment ligated inhibitor complexed with the first cyclin protein;
>
> following development of the second fragment ligated inhibitor, developing a third fragment ligated inhibitor, the third fragment ligated inhibitor differing from the peptide inhibitor by inclusion of the modified first substitute segment and also by inclusion of a second substitute segment in place of a second fragment of the peptide inhibitor, the second substitute segment being a non-

peptide fragment, the second substitute segment comprising a capping group bonded to the arginine residue or comprising a replacement for the phenylalanine residue;

determining an affinity of the third fragment ligated inhibitor for the first cyclin protein from an *in silico* model of the third fragment ligated inhibitor complexed with the first cyclin protein;

based upon the affinity, modifying the second substitute segment of the third fragment ligated inhibitor one or more times to develop a fourth fragment ligated inhibitor comprising the modified first substitute segment and the modified second substitute segment, the fourth fragment ligated inhibitor exhibiting an increased affinity for the first cyclin protein as compared to the third fragment ligated inhibitor based upon *in silico* modeling of the fourth fragment ligated inhibitor complexed with the first cyclin protein;

forming the fourth fragment ligated inhibitor *in vitro*; and

carrying out an in vitro assay to determine the inhibitory effect of the fourth fragment ligated inhibitor on the CDK/cyclin complex formed between the first CDK protein and the first cyclin protein.

Br. 14–15 (Claims Appendix).

REJECTIONS MAINTAINED ON APPEAL

1. Claims 1–5 and 7 stand rejected under 35 U.S.C. § 103 as unpatentable over Liu,[2] Andrews,[3] and Sintchak.[4] Ans. 3.

---

[2] Liu et al., *Structural and Functional Analysis of Cyclin D1 Reveals p27 and Substrate Inhibitor Binding Requirements*, 5 ACS CHEM. BIO. 1169 (2010).
[3] Andrews et al., *REPLACE: A Strategy for Iterative Design of Cyclin-Binding Groove Inhibitors*, 7 CHEMBIOCHEM 1909 (2006).
[4] Sintchak & Nimmesgern, *The Structure of Inosine 5'-monophosphate Dehydrogenase and the Design of Novel Inhibitors*, 47 IMMUNOPHARM. 163 (2000).

2. Claims 1, 2, 4, 5, and 7 stand rejected for non-statutory double patenting as unpatentable over claims 1, 3, 8–12 and 14 of the ’072 patent[5] in view of Sintchak. Ans. 9.

DISCUSSION

A. Rejection 1

The Examiner relies on a combination of Liu, Andrews, and Sintchak to reject claims 1–5 and 7 as unpatentable under § 103. *See* Non-Final Action 3–8; Ans. 3–8. We adopt the Examiner’s findings and conclusions as set forth in the Final Action and Answer, as further discussed below.

1. Teachings of the References Individually

Appellants argue generally that none of the references teaches or suggests the type of iterative[6] method, using successive rounds of *in silico* modeling, recited in claim 1. *See* Br. 7–11. Specifically, Appellants argue the modified inhibitors in Liu “were *synthesized* and were not *modeled*,” nor were the modified inhibitors subsequently optimized via *in silico* affinity determination. Br. 7. Appellants further assert that Andrews’ iterative method amounts to a “plug-and-chug” approach, in which each of 4,500 potential capping groups were modeled and scored in each of 10 different poses, resulting in 45,000 virtual screenings. *Id.* at 7–8. In contrast, Appellants describe their claimed method as utilizing “an *in silico* affinity determination in order to modify and thus optimize a single non-peptide

---

[5] McInnes et al., US 8,566,072 B2, issued Oct. 22, 2013.

[6] Claim 1 does not use the word “iterative.” However, both Appellants and the Examiner use this term in describing the claimed method and in comparing it to the prior art, as discussed herein.

fragment." *Id.* at 8. Appellants also distinguish Sintchak's iterative method as being one that "simply looks at the structure and activity information of each of these multiple different compounds one by one in an iterative fashion." *Id.* at 10.

The Examiner agrees that Liu does not disclose "an iterative method where a modified peptide is modeled *in silico* for binding, and iteratively changed based on the modeling," and further acknowledges that Andrews "does not provide an example of an iterative technique (testing thousands of modifications to a peptide individually, as noted by applicants)." Ans. 7. However, the Examiner finds that Andrews suggests an iterative methodology based on rounds of *in silico* modeling, as "the authors [of Andrews] explicitly state that the best compounds they had discovered could be further modified using similar techniques to provide improved properties." Ans. 7; *see also id.* at 5 (citing Andrews 1913). We discern no error in this interpretation of Andrews. In the paragraph cited by the Examiner (*see* Ans. 5), Andrews suggests that compounds designed through its strategy "could be considered as fragment starting points for further discovery and optimization by using REPLACE[[7]] and/or traditional medicinal chemistry/structure-guided design in order to improve potency" (Andrews 1913).

---

[7] REPLACE (REplacement with Partial Ligand Alternatives) is the drug-design strategy described in Andrews "in which nonpeptidic surrogates for specific determinants of known peptide ligands are identified *in silico* by using a core peptide-bound protein structure as a design anchor." Andrews Abstract.

As to Sintchak, the Examiner considers Appellants' reading to be overly strained, as Sintchak describes not only "the *in silico* modeling of representative commercially available compounds, identifying lead compounds," but also synthesis, testing, and modeling of lead compound analogs *in silico* "to guide further rounds of ligand design in an iterative process." Ans. 8 (discussing Sintchak 178). We agree with the Examiner that Sintchak thus discloses "a repetitive method where analogs are made, modeled in silico for insights into binding, and modified based on those insights, with the method repeated as needed until analogs with desired properties are arrived at." *Id.*

2. *Motivation to Combine*

Appellants also argue that the Examiner fails to provide a rationale for combining Sintchak with either Liu or Andrews. *See* Br. 11. Appellants note that Sintchak focuses on discovery of potential inhibitors that are "structurally unrelated to" known inhibitors for its target, IMPDH (Br. 12 (citing Sintchak 167)), in contrast to the approaches in Liu and Andrews, which start with known CDK/cyclin inhibitors (*id.*). Appellants also point out that the known inhibitors for IMPDH are not peptide inhibitors, as they are for CDK/cyclin, but rather non-polymeric molecules. *Id.* at 11 (citing Sintchak 165). Thus, according to Appellants, based on Liu and Andrews, "in which only a fragment of a known polymeric peptide inhibitor is modified in development of a new inhibitor," it would not have been obvious for the skilled artisan to look to Sintchak, "in which a library of non-polymeric molecular compounds unrelated to known inhibitors are examined for potential use as an inhibitor. Br. 12.

These arguments are unpersuasive. At the outset, Appellants' detailed distinctions regarding the types of molecules modeled in Sintchak are not salient given the very general purpose for which the Examiner relies on Sintchak, i.e., to "show[] that an iterative design methodology using computer modeling, similar to the process described by the instant claims, can accelerate the drug discovery process." Non-Final Action 5. Further, we agree with the Examiner that:

> None of the differences pointed out by applicants call into question the teachings of Liu et al and Andrews et al that specific modifications to peptides binding to the various cyclin proteins can improve their properties, the suggestion to iteratively model and modify these compounds, presented in Andrews et al, or the teachings of Sintchak et al that such methods are important (and thus well known) in the art of drug design (leading to a reasonable expectation of success). Nor do they contradict the motivation to combine, which was given by both Liu et al and Andrews et al.

Ans. 8.

3. Conclusion

Having considered each of Appellants' arguments, we are unpersuaded that the Examiner erred in rejecting claim 1 as unpatentable over Liu, Andrews, and Sintchak. Accordingly, we affirm the rejection of claim 1. Claims 2–5 and 7 are not argued separately, and fall with claim 1. *See* 37 C.F.R. § 41.37(c)(1)(iv).

B. Rejection 2

Appellants do not dispute the Examiner's non-statutory double patenting rejection of claims 1, 2, 4, 5, and 7. *See* Br. 13. We summarily affirm this rejection.

CONCLUSION

The rejections of claims 1–5 and 7 are affirmed. No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED